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Design of the INPULSIS™ trials: Two phase 3 trials of nintedanib in patients with idiopathic pulmonary fibrosis

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Summary
Background: Nintedanib is in clinical development as a treatment for idiopathic pulmonary fibrosis (IPF). Data from the Phase II TOMORROW study suggested that nintedanib 150 mg twice daily had clinical benefits with an acceptable safety profile.

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Protein kinase inhibitor;
Protein tyrosine kinases

Methods: The INPULSIS™ trials are replicate Phase III, randomized, double-blind, studies comparing the efficacy and safety of nintedanib 150 mg twice daily with placebo in patients with IPF. Eligible patients were aged ≥40 years with a diagnosis of IPF within 5 years before randomization who had undergone a chest high-resolution computed tomography (HRCT) scan within 1-year before screening, and who had a forced vital capacity (FVC) of ≥50% predicted and a diffusing capacity for carbon monoxide of 30—79% predicted. Participants were randomized 3:2 to receive nintedanib or placebo for 52 weeks. The primary endpoint is the annual rate of decline in FVC. The key secondary endpoints are change from baseline in the total score on the St. George's Respiratory Questionnaire (a measure of health-related quality of life) over 52 weeks and time to first acute exacerbation.
Results: Enrolment of 1066 patients in 24 countries was completed in September 2012. Results will be reported in the first half of 2014.
Conclusion: The INPULSIS™ trials will determine the efficacy of nintedanib in patients with IPF, including its impact on disease progression as defined by decline in FVC, acute exacerbations and health-related quality of life. In addition, they will characterise the adverse event profile of nintedanib in this patient population.
Trial registration: Registered at ClinicalTrials.gov (identifiers: NCT01335464 and NCT01335477).

Introduction

Idiopathic pulmonary fibrosis (IPF) is a specific form of chronic, progressive fibrosing interstitial pneumonia [1]. An accurate diagnosis of IPF requires the exclusion of other known causes of interstitial lung disease, the presence of a specific radiological pattern of usual interstitial pneumonia (UIP) determined by high-resolution computed tomography (HRCT), or specific combinations of HRCT and histopathologic patterns in patients who have undergone surgical lung biopsy [1]. IPF is considered a rare disease [2]. In a retrospective cohort study conducted in the United States using data from a large healthcare claims database spanning a 5-year period, the prevalence of IPF was estimated to be 14 to 43 cases per 100,000, and the annual incidence to be 6.8 to 16.3 per 100,000, depending on how cases were defined [3]. Similarly, in the United Kingdom, the annual incidence of IPF was estimated to be 7.4 per 100,000 based on primary care data from 2000 to 2008 [4]. IPF is ultimately a fatal disease, with a reported median survival time of approximately 3 years from diagnosis [5]. In addition, the symptoms of IPF impact negatively on patients' physical function and emotional well-being, as well as their health-related quality of life (HRQoL) [6,7].

An improved understanding of the pathogenic mechanisms underlying IPF over the last decade has resulted in several agents being evaluated in clinical trials [8] and in pirfenidone being approved for the treatment of a subgroup of patients with IPF in several countries. Results of four large randomized, double-blind, placebo-controlled Phase III trials investigating the efficacy and safety of treatments for IPF are awaited this year: the PANTHER-IPF trial of N-acetylcysteine (NAC) (NCT00650091), the ASCEND trial of pirfenidone (NCT01366209), and the INPULSIS™ trials of nintedanib (NCT01335464 and NCT01335477).

Nintedanib (formerly known as BIBF 1120) is a potent tyrosine kinase inhibitor targeting intracellular receptors of fibroblast growth factor receptor (FGFR), platelet-derived growth factor receptor (PDGFR), and vascular endothelial growth factor receptor (VEGFR) [9]. Activation of these receptor kinases has been implicated in multiple pathways in the pathogenesis of IPF [10,11]. *In vitro* studies and animal models suggest that nintedanib has anti-fibrotic and anti-inflammatory effects that may attenuate the progression of fibrosis [12,13]. Results from the Phase II TOMORROW trial suggested that 12 months' treatment with nintedanib 150 mg twice daily results in a reduced rate of decline in forced vital capacity (FVC), fewer acute exacerbations and preservation of HRQoL, measured using the St. George's Respiratory Questionnaire (SGRQ) [14]. The purpose of this manuscript is to describe the design of the INPULSIS™ studies, two replicate Phase III trials that further investigate the efficacy and safety of nintedanib 150 mg twice daily compared with placebo in patients with IPF.

Methods

Trial design

Both the INPULSIS™ trials are multinational, randomized, double-blind, parallel-group studies comparing the efficacy and safety of nintedanib 150 mg twice daily with placebo in patients with IPF. The INPULSIS™ trials were initiated in May 2011 and enrolment (n = 1066) was completed in September 2012. Patients were recruited in 24 countries in the Americas, Europe, Asia and Australia. Following a screening period, eligible patients were randomized 3:2 (using an interactive phone/web response system) to receive nintedanib or placebo for 52 weeks (Fig. 1). Each study concluded with a 4-week follow-up period after completion of the 52-week treatment period. A 3:2 ratio was chosen to aid enrolment. In order to reduce the amount of missing data, patients who discontinued trial drug, for any reason, prior to completing the 52 weeks' treatment were asked to attend all visits and undergo all examinations

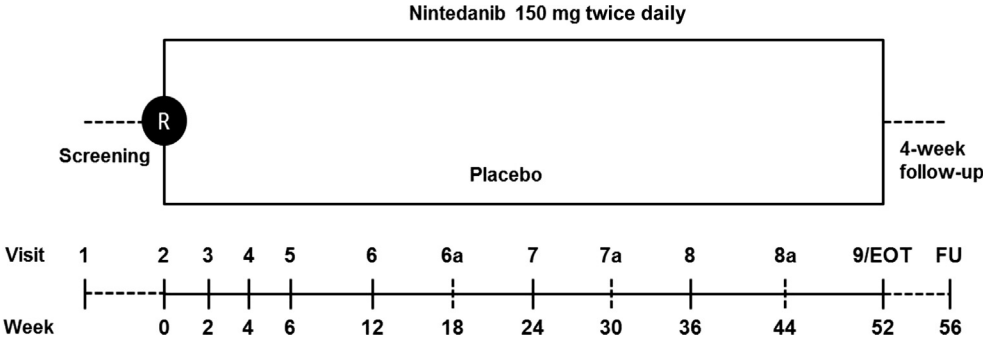

Figure 1 INPULSIS™ trial design. R, randomization (3:2 ratio for nintedanib:placebo); EOT, end of treatment; FU, follow-up. FVC was measured at all visits except visits 6a, 7a and 8a, which were for blood sampling for laboratory tests only.

as originally planned. In addition, vital status at week 52 was to be collected for all patients who prematurely discontinued but did not agree to attend all visits until week 52.

For each trial, the sample size was calculated to provide 90% power to detect a difference of 100 mL/year between the treatment groups in the rate of FVC decline. Based on the Phase II TOMORROW trial data, the common standard deviation for change from baseline in FVC was assumed to be 300 mL. Assuming data from 2% of patients would be non-evaluable, the sample size was calculated as 194 patients in the placebo group and 291 patients in the nintedanib 150 mg twice daily group if using a 2 group *t*-test at a 1-sided 2.5% level. Since the primary analysis is a random coefficient regression model, including adjustment for several variables and taking into account information across time rather than at a single time-point, it is expected that the power will be greater than the 90% calculated for the *t*-test.

As in the Phase II TOMORROW trial, dose interruption and/or reduction of the dose from 150 mg twice daily to 100 mg twice daily was allowed for the management of adverse events. After an adverse event had resolved, the dose could be reinstituted at 150 mg twice daily. The investigators were provided with guidelines on the management of diarrhoea, a known side-effect related to treatment with tyrosine kinase inhibitors [15,16]. Guidelines on the management of liver enzyme elevations were also provided to the investigators. Patients who completed the 52-week treatment period and the 4-week follow-up period in the INPULSIS™ trials were invited to participate in an open-label extension trial (NCT01619085).

Trial organisation and oversight

The INPULSIS™ trials were guided by an advisory committee consisting of clinical experts in IPF and representatives of the sponsor, Boehringer Ingelheim. An independent Data Monitoring Committee (DMC) regularly reviewed the data, in particular serious adverse events, adverse events leading to discontinuation of study drug, and laboratory parameters, and made recommendations to the sponsor about the continuation of the trials. An Adjudication Committee reviewed medical documentation for all deaths to evaluate the primary cause of death in a blinded manner. This committee also adjudicated all events reported by the investigators as meeting the criteria for an acute exacerbation of IPF as defined in the protocol, classifying them as a confirmed acute exacerbation, suspected acute exacerbation, or not an acute exacerbation.

Both trials were conducted in accordance with the principles of the Declaration of Helsinki and the Harmonized Tripartite Guideline for Good Clinical Practice from the International Conference on Harmonization and were approved by local authorities. The clinical trial protocol was approved by an Independent Ethics Committee and/or Institutional Review Board at all the participating centres. All patients provided written informed consent prior to study entry.

Patients

To be eligible to participate in the INPULSIS™ trials, patients had to be $\geq$40 years of age with a diagnosis of IPF established within 5 years before randomization, to have undergone chest HRCT within 12 months before screening, and to have an FVC $\geq$50% of predicted value [17] and a carbon monoxide diffusion capacity (DL_{CO}) of 30—79% of predicted value [18]. The diagnosis of IPF was established based on the central review of chest HRCT scans from all patients by an expert radiologist (DMH) according to protocol-specified criteria (Table 1). Surgical lung biopsy specimens were also centrally evaluated if available by an expert pathologist (AGN).

Table 1 Diagnostic criteria for IPF based on chest HRCT if surgical lung biopsy was not available. To qualify for a diagnosis of IPF if a surgical lung biopsy was not available, the criteria A and B and C; or criteria A and C; or criteria B and C had to be met.

A	Definite honeycomb lung destruction with basal and peripheral predominance
B	Presence of reticular abnormality and traction bronchiectasis consistent with fibrosis with basal and peripheral predominance
C	Atypical features are absent, specifically nodules and consolidation. Ground glass opacity, if present, is less extensive than reticular opacity pattern

Patients with abnormal laboratory parameters (liver transaminases or bilirubin above 1.5-fold upper limit of normal), cardiac disease (i.e. myocardial infarction within 6 months or unstable angina within 1 month of randomization), or who, in the opinion of the investigator, were likely to receive a lung transplant during the study were not permitted to enter the trial. Patients who were taking full-dose anticoagulant therapy or high-dose antiplatelet therapy at screening, or had received treatment with NAC or prednisone >15 mg/day or equivalent within 2 weeks of screening, or pirfenidone, azathioprine, cyclophosphamide, cyclosporine A or any investigational drug within 8 weeks of screening, were excluded. Concomitant therapy with prednisone ≤15 mg/day or equivalent was permitted if the dose had been stable for ≥8 weeks prior to screening. Patients who experienced deterioration, as judged by the investigator, were permitted to receive concomitant treatment with azathioprine, cyclophosphamide, cyclosporine A, NAC, or prednisone >15 mg/day or equivalent at the discretion of the investigator 6 months or more after starting to receive study medication. In cases of acute exacerbation, any treatments could be freely initiated or increased as deemed appropriate by the investigator. However, pirfenidone and any investigational treatments for IPF were not allowed throughout the trial.

Outcome measures

The primary endpoint for the INPULSIS™ trials is the annual rate of decline in FVC (mL/year), calculated from measurements obtained over the 52 weeks of treatment (Fig. 2). Spirometry testing was conducted according to ATS/ERS criteria, including daily calibration of the spirometer, regular calibration of the calibration pump and FVC tests conducted in triplicate, with the highest result selected [19]. All spirometry was performed on sponsor-provided machines and ongoing feedback and training were provided.

The key secondary endpoints are change from baseline in SGRQ total score over 52 weeks and time to first acute exacerbation. Acute exacerbations were defined as events meeting all of the following criteria: unexplained worsening or development of dyspnoea within 30 days, new diffuse pulmonary infiltrates on chest X-ray and/or HRCT, or parenchymal abnormalities with no pneumothorax or pleural effusion (new ground-glass opacities) since last visit. Causes of the acute worsening, including infection, left heart failure, pulmonary embolism or any identifiable cause of acute lung injury were to be excluded as per routine clinical practice and microbiological studies. Investigator-reported exacerbations were adjudicated by the Adjudication Committee. Other secondary endpoints include absolute changes from baseline in FVC (mL and % predicted); proportion of FVC responders (patients who did not have an absolute decline in FVC % predicted of >5% or >10%); risk of an acute exacerbation; change from baseline in SpO_2 (oxygen saturation) at rest; change from baseline in DL_{CO} at rest (measured in accordance with ATS/ERS guidelines [20]); all-cause, respiratory, and 'on-treatment' time to death. Composite endpoints of time to death or lung transplant, and time to death or lung transplant or meeting arbitrary pre-defined criteria for lung transplant (FVC <45% predicted *or* DL_{CO} <30% predicted *or* SpO_2 <88% at rest) were also included in order to capture a range of outcomes indicating an unfavourable clinical course.

Further patient-reported outcomes (PROs) investigated in the INPULSIS™ trials are the change from baseline to week 52 in the score on the three SGRQ domains (impact, symptoms, activity) [21], SGRQ-I [22], University of California San Diego Shortness of Breath Questionnaire [UCSD-SOBQ] [23], EuroQol 5-dimensional quality of life questionnaire [EQ5D], Cough and Sputum Assessment Questionnaire cough domains [CASA-Q(CD)] [24]; the proportion of 4-point responders on SGRQ total score; and the proportion of responders on Patient's Global Impression of Change (PGI-C). Safety assessment will include reporting of

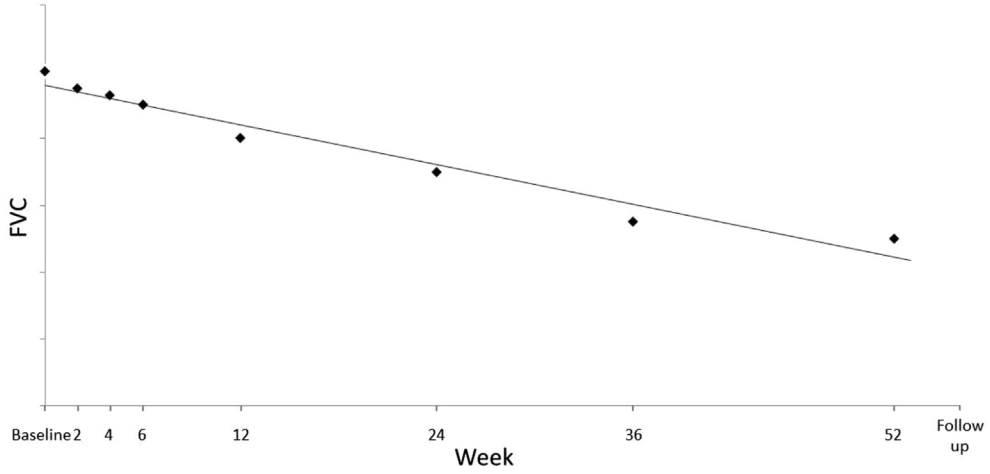

Figure 2 Methodology for calculating slope of FVC decline. The primary endpoint will be analysed using a random coefficient regression (random slopes and intercepts) model, including gender, age and height as covariates. Visits are planned at 2, 4, 6, 12, 24, 36 and 52 weeks after randomization. All available FVC values except the value from the follow-up visit will be used in this analysis except for patients who prematurely discontinue trial medication, in which case the value from the follow-up visit will also be used.

adverse events; assessment of vital signs, physical examination and weight; clinical laboratory tests (haematology, clinical chemistry and urinalysis).

Statistical analysis

Efficacy and safety analyses will be conducted on patients who were randomized to treatment (nintedanib or placebo) and received ≥1 dose of study medication. The annual rate of decline in FVC will be primarily analysed using a random coefficient regression (random slopes and intercepts) model including gender, age and height as covariates. All available FVC values from baseline to week 52 will be used in the primary model, including FVC measurements from the follow-up visit for patients who prematurely discontinued trial medication and did not complete study visits until week 52. A linear model was chosen as in this patient population, FVC is expected to decline linearly over time. However, a number of alternative and sensitivity analyses have been pre-specified in the statistical analysis plan, such as change from baseline to week 52 in FVC and other functional forms for the rate of decline (quadratic and exponential) to assess the robustness of the linear model. Model assumptions also include a normal distribution for the intercepts and slopes with an arbitrary covariance matrix. An unstructured variance-covariance structure will be used to model within-patient measurements. The variance-covariance matrix, modeled to estimate the inter-individual variability, will be considered to have a Variance-Components structure. The Roger-Kenward approximation will be used to estimate denominators degrees of freedom.

Change from baseline in SGRQ total score over 52 weeks will be primarily analysed using mixed model repeated measures (MMRM) with treatment and visit as fixed effects, baseline SGRQ total score as a covariate, and treatment-by-visit and baseline-by-visit as interaction terms. The patient effect will be assumed to be random and compound symmetry covariance structure will be assumed for within-patient variation.

Kaplan–Meier estimates will be derived for the probability of a first acute exacerbation over time, and time to first acute exacerbation will be primarily analysed using the log rank test. The hazard ratios and their confidence intervals will be computed using a Cox proportional hazards model adjusted for gender, age and height. These covariates were chosen in order to be consistent with the analyses performed in the Phase II TOMORROW trial [14] and are the same covariates as included in the primary endpoint model. The key secondary endpoint uses data on acute exacerbations as reported by the site investigators, in keeping with the Phase II methodology. Events adjudicated as confirmed or suspected acute exacerbations by the Adjudication Committee will be assessed in a sensitivity analysis of data pooled from both INPULSIS™ trials.

A hierarchical procedure will be used to demonstrate the superiority of nintedanib over placebo for the primary and key secondary endpoints. The consecutive steps of the hierarchy will only be considered if the previous step is significant at the 1-sided 2.5% level and the results are in favour of nintedanib. Two hierarchies of endpoints, with a different order of the key secondary endpoints for submissions to US and EU/rest of world regulatory authorities, will be tested. For the US submission, time to first acute exacerbation is the first key secondary endpoint; for the EU/rest of world submissions, change from baseline in SGRQ total score over 52 weeks is the first key secondary endpoint. No hierarchy will be used for the other secondary endpoints.

Absolute and relative changes from baseline in FVC over 52 weeks will be analysed using MMRM, with treatment and visit as fixed effects and baseline value, gender, age and height as covariates, and treatment-by-visit and baseline-by-visit as interaction terms. Changes in other respiratory parameters will be analysed in the same way as change in FVC. Changes in other PROs will be analysed in the same way as change in SGRQ total score.

For the survival analyses, a log rank test will be used to compare treatment groups and a Cox model adjusted for gender, age and height will be used to determine hazard ratios. These covariates were chosen in order to be consistent with the analyses performed in the Phase II TOMORROW trial [14] and are the same covariates as included in the primary endpoint model. Since the number of deaths is expected to be low, the protocol specified that survival analyses will additionally be performed on the pooled data from both INPULSIS™ trials. Safety analyses will be descriptive.

Sensitivity analyses will be performed to assess the robustness of the results of the primary and key secondary endpoints. Model assumptions will be checked and sensitivity to data handling, including missing data handling, will be assessed. In order to improve the precision of the treatment effect estimates for the efficacy endpoints and to increase the size of the safety database, a pooled analysis of the two trials was pre-specified as an additional supportive analysis.

Discussion

Rationale for dose selection

The dose of nintedanib used in the INPULSIS™ trials was selected based on findings from the 12-month Phase II TOMORROW study [14]. In the TOMORROW trial, the annual rate of decline in FVC in the nintedanib 150 mg twice daily group was −0.06 L (95% CI, −0.14 to 0.02) compared with −0.19 L (95% CI, −0.26 to −0.12) in the placebo group: a difference of 0.13 L (95% CI, 0.03–0.24). In addition, treatment with nintedanib 150 mg twice daily was associated with preservation of HRQoL (mean change in SGRQ total score of −0.66 [95% CI, −4.02 to 2.71] versus 5.46 [95% CI, 2.06, 8.86] with placebo: a difference of −6.12 [95% CI, −10.57 to −1.67]) and a reduction in the risk of acute exacerbations (risk ratio compared with placebo: 0.16 [95% CI, 0.03 to 0.70]).

Rationale for endpoints

The most robust primary endpoint for Phase III clinical trials in IPF is all-cause mortality [25]. However, the mortality rate of patients enrolled in the TOMORROW trial was low,

and it was assessed that it was not feasible to use mortality as the primary endpoint in the INPULSIS™ trials. Based on the 1-year survival rates observed in the TOMORROW study (89.2% of patients in the placebo group and 91.7% of patients in the nintedanib 150 mg twice daily group) it was calculated that a 1-year trial would require the inclusion of a total of approximately 6000 patients to provide 90% power to detect a difference between groups with a 2-sided *p*-value of 5%.

In the absence of an alternative explanation, a decrease in FVC in patients with IPF is consistent with progressive disease [1] and has been shown to be associated with reduced survival time in patients with IPF [26—32]. Change in FVC over 1 year has been used as a primary endpoint for Phase III clinical trials in patients with IPF [25,33]. The annual rate of decline in FVC — the primary endpoint in the INPULSIS™ trials — uses all the FVC values collected during the trial. This was considered to be a more robust methodology than using only the FVC value from baseline and 52 weeks because it enables calculation of the rate of decline even in patients without a week 52 value.

Several PROs for the assessment of the symptoms of IPF and the broader construct of HRQoL have been included as secondary endpoints in the INPULSIS™ trials. The SGRQ, chosen as a key secondary endpoint in the INPULSIS™ trials, has demonstrated acceptable psychometric characteristics in patients with IPF, including construct validity, reliability, and ability to detect change over time [22,34—36]. The two PROs used to assess dyspnoea, the UCSD-SOBQ and CASA-Q (CD), have been shown to have content validity in patients with IPF [37], with the UCSD-SOBQ also shown to detect change over time [36,38].

In the INPULSIS™ trials, acute exacerbations reported by the investigators will be assessed as a key secondary endpoint, as was done in the Phase II TOMORROW trial, in which a clinically relevant efficacy signal on acute exacerbations was observed. Furthermore, recent data suggest that suspected acute exacerbations (events that the investigator thinks are acute exacerbations but that cannot be adjudicated as acute exacerbations due to missing data or criteria) are clinically indistinguishable from confirmed acute exacerbations defined according to the consensus diagnostic criteria [39] and that both are clinically meaningful events [40]. Investigator-identified acute exacerbations were felt to best capture both definite and suspected acute exacerbations.

Conclusions

The INPULSIS™ trials will investigate the efficacy of nintedanib in patients with IPF, including its impact on disease progression as defined by decline in FVC, acute exacerbations and HRQoL. In addition, the data collected will characterise the adverse event profile of nintedanib in this patient population. The INPULSIS™ trials will report results in the first half of 2014. Together with the results of the other large ongoing randomized placebo-controlled trials in IPF, the INPULSIS™ trials will add significantly to scientific understanding of the natural history of IPF and will have potential implications for disease management.

Conflicts of interest

The INPULSIS™ trials were funded by Boehringer Ingelheim.

Luca Richeldi has received grants for research and fees for lectures, advisory boards meetings, and steering committee meetings from InterMune, Boehringer Ingelheim, Roche, Takeda, Shionogi, Biogen Idec, Sanofi-Aventis, MedImmune and ImmuneWorks.

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Martin Kolb has received consulting fees from Boehringer Ingelheim, InterMune and GlaxoSmithKline for activities related to IPF and his institution has received research grants from Boehringer Ingelheim, InterMune and GlaxoSmithKline.

Hiroyuki Taniguchi has received consultancy fees from Boehringer Ingelheim for steering committee meetings and advisory board meetings and from Olympus Corporation and AstraZeneca for advisory board meetings. He has received fees for lectures from Shionogi, Boehringer Ingelheim, Asahi Kasei Pharma Corp, Bayer, Chugai, GlaxoSmithKline, Ono Pharmaceutical Co, Teijin Pharma, AstraZeneca, Daiichi Sankyo, Eli Lilly, Novartis, Fukuda Denshi Co, Terumo Corp, Taiho Pharmaceutical Co, Kyorin Pharmaceutical Co, Meiji Seika Pharma Co, Philips Respironics, Pfizer, Abbott, Nippon Shinyaku Co, Eisai and Merck Sharp & Dohme.

David M. Hansell has received fees for consultancy and evaluating CT scans from Boehringer Ingelheim, InterMune and AstraZeneca.

Andrew G. Nicholson has no competing interests.

Ganesh Raghu has received travel reimbursements from Boehringer Ingelheim to attend scientific advisory board meetings.

Florence Le Maulf and Susanne Stowasser are employees of Boehringer Ingelheim.

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Authors' contributions

All authors contributed to the study design and/or discussions regarding how the data from these trials would be analysed and interpreted. All authors contributed to the development of the manuscript. All authors have approved the final manuscript.

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